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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,272	07/03/2003	Mark J. Mamula	102321-201	4375

27267 7590 12/31/2008

WIGGIN AND DANA LLP
ATTENTION: PATENT DOCKETING
ONE CENTURY TOWER, P.O. BOX 1832
NEW HAVEN, CT 06508-1832

EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
12/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/613,272	MAMULA, MARK J.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,10-14,17-22 and 25-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,2,4,5,10,19-22 and 25* is/are allowed.

6)☒ Claim(s) *11-14,17,18 and 26-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/3/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim 26 has been amended. Claims 1, 2, 4, 5, 10-14, 17-22 and 25-28 are pending and under consideration.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for carriers consistent with dosage forms which are parenteral, does not reasonably provide enablement for carriers consistent with dosage forms which are enteral or topical. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

Claims 27 requires a carriers which is a sublingual lozenge or an enema solution, and thus encompasses an oral and anal route of immunization. Claim 27 requires a solid carrier material consistent with an anal suppository. The art teaches that a condition or oral tolerance develops for many antigens presented by the oral route and that this is a natural phenomenon believed to be functioning for the preventing the immune system from responding to food antigens and normal microbial flora (Nossal, Annual Review in Immunology, 1983, vol. 1, pp. 33-63). The art teaches that although most antigens administered orally induce tolerance, in a few cases oral immunization confers immunity to pathogens such as poliovirus (Sabin et al, JAMA, 1984, vol. 251, pp. 2988-2993) and V. cholerae (Lycke et al, Sandinavian Journal of Immunology, 1987, Vol. 25, pp. 407-412). Further, Smith et al (Immunology, 2002, Vol. 106, pp. 144-158) published an article wherein it was stated in the abstract:

How the mucosal immune system promotes active immunity against harmful organisms but tolerance to commensal bacteria or dietary antigens is poorly understood. Thus, the antigen-presenting cell (APC), site of antigen presentation, and effector mechanisms responsible for oral

priming and tolerance remain unclear. Characterizing differences between oral priming and tolerance may improve the exploitation of oral tolerance for therapeutic applications and aid the design of oral vaccines.

Thus, it is concluded that at the time of filing, the state of the art with regard to the induction of immunity by oral administration of antigen was undeveloped. Further, the same considerations regarding tolerance to commensual bacteria and dietary antigens would apply to anal administration of an antigen, encompassed by the anal suppositories, solid carrier material,, melting waxes and enema solutions of claims 27 and 28 . The specification does not address this issue and fails to teach how to reliably overcome the induction of tolerance versus immune response by the oral administration route. One of skill in the art would be subject to undue experimentation in order to use the compositions having formulations consistent with oral or anal administration.

Claim 27 requires a carrier which is a topical; cream; claim 28 requires a carrier which is cocoa butter, both of which are consistent with the topical administration of the protein of claim 26. the art recognizes the peptides and proteins do not penetrate the stratum corneum and therefore the topical administration of proteins and peptides is generally hampered because of low absorption from the application site (Njieha et al, U.S. 5,070,188, column 1, lines 24-27). The specification fails to teach how a carrier which is a topical cream or cocoa butter can provide a humoral immune response to the isoaspartyl modified peptide of claim 26. One of skill in the art would be subject to undue experimentation in order to make and use the broadly claimed pharmaceutical carriers in conjunction with the isoaspartyl modified protein of claim 26,

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11-14, 17, 18, 26-28 rejected under 35 U.S.C. 103(a) as being unpatentable over Mamula et al (Journal of Biological Chemistry, 1999, vol. 274, pp. 22321-22327) in view of the abstract of Disis et al (Critical Reviews in Immunology, 1998, vol. 18, pp. 37-45) and Slingluff et al (WO 97/34613).

Claim 11 is drawn in part to a method of enhancing the humoral immune response of a patient relative to the normal humoral immune response comprising the steps of administering to said patient a peptide comprising 9-40 amino acid residues to a tumor antigen, wherein said peptide comprises an aspartic acid residue or asparagine residue that has been replaced with an isoaspartic acid residue. Claim 12 embodies the method of claim 11 wherein said peptide comprises 9-25 amino acid residues. Claim 13 embodies the method of claim 11 wherein said peptide comprises 9-15 amino acid residues. Claim 14 embodies the method of claim 11 wherein said tumor antigen is selected from a group including tyrosinase. Claim 17 embodies the method of claim 11 wherein said aspartic acid residue or asparagine residue forms part of an amino acid sequence selected from a group including Asp-Gly. Claim 18 embodies the method of claim 11 wherein said peptide has the sequence YMDGTMSQV.

Claim 26 is drawn to a composition comprising a protein selected from a group including tyrosinase and a pharmaceutically acceptable carrier. claim 27 embodies the composition of claim 26 wherein the carrier is an electrolyte solution. Claim 28 embodies the composition of claim 26 wherein the carrier is water.

Mamula et al teach that isoaspartyl modification of self-peptides triggers an autoimmune response to self-proteins. Mamula et al teach that immunization of mice with the modified peptides in adjuvant resulted in autoantibody production (page 22322, under the heading of "Autoantibody Analysis"). Mamula et al teach that the immunizing peptides were 15-mers and 24-mers of the snRNP D peptide (page 22322, first column, under the heading of "Antigens") which meet the length limitation of claims 12 and 13. Mamula et al do not teach peptide antigens which are selected from tyrosinase, or the tyrosinase-related protein-1.

The abstract of Disis teaches that existing immunity in human melanoma has identified immune response to the non-mutated self-proteins of tyrosinase. The abstract of Disis suggests the harnessing of immunity to "self" tumor antigens for cancer therapeutics.

Slingluff et al teach the tryosinase peptide 1030, YMDGTMSQV, which reconstitutes an A2 epitope of tyrosinase and is recognized by lymphocytes (page 31, lines 20-24). The 1030 peptide of Slinghuff et al is identical to the instant SEQ ID NO:1 in claim 18.

It would have been prima facie obvious at the time the invention was made to make a pharmaceutical composition comprising the tryosinase peptide 1030, YMDGTMSQV, wherein the "D" was substituted for an isoaspartly residue by amino acid synthesis. It would be further obvious to provide said peptide in sterile saline or sterile non-pyrogenic water for ease of handling and storage. One of skill in the art would have been motivated to do so by the teachings of Disis regarding the existence of an immune response to non-mutated tyrosinase in melanoma patients and the teachings of Slinghuff regarding the immunogenic epitope of tyrosinase. One of skill in the art would understand that increasing the immune response to tyrosinase by the administration of the tyrosinase peptide modified by the substitution of an isoaspartyl residue would boost the already existent immune response to tyrosinase in melanoma patients and thus provide a means for harnessing immunity to "self" tumor antigens as suggested by the abstract of Disis.

Claims 1, 2, 4, 5, 10, 19-22 and 25 are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/
Primary Examiner, Art Unit 1643